# Local treatment in young breast cancer patients

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# Chapter 8

Summarizing discussion
and future perspectives

# Summarizing discussion

In this thesis we reported on our research on the value of breast-conserving therapy (BCT, *i.e.*, lumpectomy followed by radiotherapy) in young women with early stage breast cancer with regard to clinical outcomes, treatment-related toxicities and quality of life. Although young patients constitute a relatively small subgroup of all breast cancer cases, 700 cases are reported annually in the Netherlands. They also face several specific issues in the course of their disease.

After breast cancer has been diagnosed, one of the choices to be made is the type of local treatment. Options include mastectomy, with or without direct reconstruction, and BCT. For all age groups, survival after mastectomy and BCT is similar [1, 2], although young age is a known risk factor for local recurrence and distant relapse after both BCT and mastectomy. The risk of local recurrence after BCT is also higher than after mastectomy [3]. Nevertheless, no consensus exists about whether this difference in local recurrences translates into inferior survival after BCT in young women suffering from breast cancer [4-6]. A local recurrence is possibly a source of distant spread by itself [7-11]. Therefore, in **Chapter 2**, the effect of local treatment (BCT versus mastectomy) on overall survival (OS) was analysed in a population-based cohort of 1,453 young breast cancer patients (<40 years), with small tumours and only few involved lymph nodes (pT1N0-1M0), theoretically ideal candidates for BCT.

With a median follow-up of 9.6 years, 10-year OS was not impaired after BCT compared to mastectomy but was even better, i.e., 83% after BCT and 78% after mastectomy, respectively ($p$ = 0.007). Since outcomes of local treatment were modified by nodal stage (significant interaction), both groups were analysed separately. In node negative (N0-) patients, 10-year OS was 84% after BCT and 81% after mastectomy and local treatment was not associated with differences in OS. Within the N1-patient group, OS was better after BCT compared with mastectomy, 79% vs. 71% at 10 years ($p$ = 0.001). This difference in survival between patients treated with BCT and mastectomy might reflect the beneficial effect of radiotherapy, which was given to all BCT patients. In conventional whole breast radiotherapy with 2 tangial beams, parts of level I, II and interpectoral lymph nodes of the axilla are covered by the radiation fields [12]. One hypothesis is that the lymph node metastases positive axilla contains occult metastatic cells, which can be tackled by irradiation. The occult cells had possibly been eliminated by this unintentionally delivered irradiation, as part of BCT.

Consequently, our study results do not justify withholding BCT from women younger than 40 years with early stage breast cancer and add to the mounting evidence in favour of radiotherapy for patients with 1 to 3 lymph nodes, regardless of primary surgical treatment [13-16]. Recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a meta-analysis of 8,135 women on the effect of radiotherapy after mastectomy on recurrence and breast cancer mortality [17]. Target volumes included chest wall, supraclavicular or axillary fossa (or both), and the internal mammary chain. For 1,314 women with axillary dissection and 1 to 3 positive lymph nodes, radiotherapy significantly reduced locoregional recurrence ($p$ < 0.0001), overall recurrence

(relative risk (RR) 0.68, 95% confidence interval (CI) 0.57-0.82) and breast cancer mortality (RR 0.80, 95% CI 0.67-0.95), even when systemic therapy was given. However, since the risk of locoregional recurrence has decreased markedly during the last two decades due to improved axillary surgery techniques and addition of more effective systemic therapy [18, 19], the absolute benefit of the addition of radiotherapy after mastectomy in women treated today might be smaller than in the older trials included in this meta-analysis [17]. The definitive answer to this question is expected to be provided by the recently closed phase III Selective Use of Post Mastectomy Radiotherapy (SUPREMO) trial, which investigated the benefit of radiotherapy after mastectomy in patients with 1-3 positive lymph nodes [20].

In the SUPREMO trial, this intermediate risk group was treated with chest wall irradiation alone, hereby indirectly addressing the question about the extent of post-mastectomy radiotherapy. It is currently unknown whether full locoregional radiotherapy provides additional benefit beyond chest wall irradiation alone. One consideration is that in locoregional radiotherapy the axillary fields are responsible for increasing treatment-related toxicity, such as lung fibrosis, brachial plexopathy, shoulder dysfunction, and arm oedema [21]. In women with unfavourable node-negative or node-positive disease treated with breast-conserving surgery and systemic therapy, the MA20 trial investigated the effect of adding regional radiotherapy to standard breast radiotherapy [22]. The results of this trial are expected to be published in 2015.



Since the study described in Chapter 2 was cancer-registry based, no data on local recurrences and other known risk factors for relapse were available. In the retrospective study presented in **Chapter 3**, several other important endpoints, such as tumour recurrence, distant relapse and death with the corresponding dates, were collected from 536 young breast cancer patients (≤ 40 years) (pT1N0-3M0) in the Northern region of the Netherlands. The following research questions were addressed: 1) compared with mastectomy is BCT associated with a negative outcome in terms of distant metastases or death (DMD)? 2) what is the relationship between locoregional recurrence (LRR) and DMD?

With a median follow-up of 9.0 years, the 10-year actuarial cumulative incidence of DMD was 31% after mastectomy and 26% after BCT ($p$ = 0.04). In total, 15% LRRs were observed. After BCT, patients had a 3-fold higher risk of LRR than after mastectomy. Patients with LRR had a 5-fold higher risk of DMD compared with patients without LRR. This effect has been shown by others in all age groups, with reported risks ranging between 2.5-5.3 [7, 11, 23]. However, BCT was not adversely associated with DMD-after-LRR. In conclusion, although LRR significantly affected DMD, the increased risk of LRR after BCT compared with mastectomy did not lead to a worse DMD outcome in young breast cancer patients. The current data suggest that chest wall recurrences after mastectomy, rather than LRR after BCT, represent the highest risk of distant metastases and death in a population of young patients. This is in line with the data presented by Janni *et al.* [24]. In a matched pair analysis of 134 patients newly diagnosed with LRR (mean age of 53 years) without evidence of systemic disease, they found that LRR occurred on average 9 months earlier after mastectomy than after BCT, and that the risk of dying of breast cancer was 1.7-fold higher after mastectomy compared to after BCT.

Therefore, the results described in Chapter 3 further support the recommendation that young women should not be counselled to undergo a mastectomy based on the erroneous assumption of improved likelihood of survival. Based on the clinical outcomes, it appears safe to treat young women with BCT, as supported by the studies presented in Chapters 2 and 3. In these studies, all women were treated with 2-dimensional (2D) radiotherapy as part of BCT. Nowadays, 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) techniques are used. Planning is performed using CT, which may improve reconstruction of the exact location and volume of the tumour and offers opportunities to optimise dose homogeneity and dose conformity. The question arises as to whether these new techniques result in the same treatment outcomes compared to the 2D-era. In other words, can the outcomes obtained in the 2D-era be extrapolated to those obtained with modern radiotherapy techniques? Moreover, are treatment outcomes after 3D-CRT in young women similar to those observed in older women? Next to tumour-related outcomes it is important to evaluate the impact of these newer techniques on treatment-related toxicity.

From 2005 to 2011, patients of all ages undergoing breast-conserving surgery were irradiated post-operatively at our Radiation Oncology department with 3D-CRT with a simultaneous integrated photon boost (3D-CRT-SIB), as previously described [25]. Fractionation schemes used were 28 daily fractions of 1.8 Gray (Gy) to the whole breast and 2.3 Gy or 2.4 Gy to the surgical bed, resulting in a total dose of 64.4 Gy or 67.2 Gy, respectively. The highest boost dose was administered in case of focal positive surgical margins.



The first clinical outcomes in patients treated with 3D-CRT-SIB from 2005 to 2008 were collected retrospectively. The 3-year figures and differences in outcomes between young and older patients are presented in **Chapter 4**. At 3 years, the 3D-CRT-SIB in BCT resulted in excellent local control and overall survival rates with only few events during follow-up. Young age was not a risk factor for any recurrence. In the 5-year update (**Chapter 5**), the unadjusted 5-year actuarial rate of local control was 99%, disease-specific survival 97%, and OS 93% for the whole cohort, respectively. Also, after 5 years of follow-up, no differences in outcomes were observed between young and older patients. The observed outcomes of our cohort are comparable to those reported in the unblinded preliminary data of the Dutch Young Boost trial [26]. An increasing use of adjuvant systemic therapy combined with a better delivery of radiotherapy is considered responsible for a further reduction of LRRs [18, 27]. However, it can not be excluded that to some extent bias by indication is responsible for these excellent figures.

To evaluate clinical outcomes and toxicity based on prospective registration, we initiated a standard follow-up programme (SFP) in 2008. In the SFP, all new breast-conserved patients and all patients previously treated with BCT in yearly follow-up were included, in which toxicity, quality of life and tumour status were prospectively scored and collected.

For any patient, but in particular for young breast cancer patients, it is important not just to focus on outcome measures, such as local control and overall survival, but also on treatment-related toxicity. At present, a high proportion of young women are treated with multiple modalities including surgery, radiotherapy and systemic treatment. Treatment- related complaints can potentially impact health-related quality of life (HRQoL) (**Chapters 6 and 7**). This focus on toxicity is particularly important when a new radiotherapy technique is used, such as the 3D-CRT-SIB, which provides increased dose homogeneity, with less unintended excessive dose outside the boost area, in combination with a higher dose per fraction to the tumour bed, compared with the conventional sequential boost-techniques [25].

**Chapter 6** reports on prospectively collected physician-rated toxicity and cosmetic outcome after 3D-CRT-SIB. At 3 years, toxicity scores of 436 patients were available. Grade ≥ 2 fibrosis in the boost area was observed in 9%, non-boost fibrosis in 49%, pain to the chest wall in 7%, and fair to poor cosmetic outcome in 40% of cases.

Using multivariate logistic regression analyses, several risk factors could be identified for the various toxicity endpoints. Radiotherapy before chemotherapy was significantly associated with grade ≥ 2 boost fibrosis at 3 years. Non-boost fibrosis was associated with re-resection and larger tumours. A fair to poor cosmetic outcome was observed 4.5 times more often after re-resection, 3 times more after regional radiotherapy, and in patients with larger tumours. Age was a significant prognostic factor for only one endpoint. At 1 year, chest wall pain was significantly associated with younger age (≤ 50 years) and with high boost dosage. Younger patients had more pain complaints and used more pain medication. Similar results were found previously in a nationwide Danish survey study (28), in which younger age was associated with the development of chronic pain after breast cancer treatment. This age-related finding could be explained by the misattribution of pain and the decreased tendency to label a sensation as painful with increasing age [29].

In general, it can be stated that the hypofractionated 3D-CRT-SIB technique as part of BCT is safe regarding short-term normal tissue complications. Young age was found to be prognostic for the risk of pain to the chest wall. Cosmetic outcome was influenced most by the performance of re-resection. Fibrosis in the boost area was not associated with radiotherapy parameters. To value the reported toxicities one should take into account that all were assessed in a relatively short timeframe.

Advances of multimodality strategies in term of efficacy have resulted in a growing population of cancer survivors and may increase the number of patients suffering from transient, persisting or even progressive late side effects [30]. The occurrence of treatment-related side effects may have major impact on patient's health-related quality of life (HRQoL). After BCT, arm oedema, complaints of arm pain, breast sensitivity and fair to poor cosmetic outcome are associated with impaired quality of life [31, 32]. Furthermore, published data suggest that breast cancer has a greater impact on HRQoL in younger patients than in older ones [33-37] and a reduction in impact is seen with increasing age [38].





**Chapter 7** reports on the results of a study based on large prospective cohort (*n* = 1,420) to study the impact of age (≤ 50 years) on the changes in HRQoL in breast cancer survivors up to 5 years after radiotherapy corrected for potential confounding such as the use of chemotherapy or endocrine treatment, and second to compare HRQoL in the younger patient cohort with the general population.

Compared to their older counterparts, young women had worse HRQoL in the first year after radiotherapy as part of BCT, with small but significant clinical relevance in almost all HRQoL subscales. However, 3 years after radiotherapy, they appear to recover to the values of the normal young Dutch population. Symptoms commonly reported after radiotherapy, such as pain and fatigue were, in contrast to what is generally perceived, self-limiting, without significant differences between the young reference population and the young breast cancer patients at 3 years after radiotherapy.

Like the trends seen in the Dutch reference population, sexual functioning was best in the youngest group, followed by the middle aged, and did not improve over time in any of the age groups. At 3 years after radiotherapy, the difference in sexual functioning between the young breast cancer patients and the young reference population was not statistically significant.

These results indicate that, although initially present, on the medium long-term, young age is not a risk factor for decreased HRQoL after radiotherapy in breast cancer treatment. These findings are in agreement with those from two studies by Schroevers *et al.* [35, 38], in which HRQoL was most impacted in young cancer patients who survived several malignancies (including 50% breast cancer). The largest improvement in HRQoL was observed in the first year after diagnosis; after 8 years no significant differences in HRQoL were observed between the survivors of all ages compared to a reference population. The recently published study by Champion *et al.* [34] contradicts these results. Between 3 and 8 years after diagnosis, young breast cancer survivors (≤ 45 years; *n* = 505) reported more depressive symptoms, more fatigue, poorer self-reported attention function, and poorer sexual function compared to both older patients and age-matched controls. One explanation for the differences between our study and Champion *et al.* might be that in our study quality of life outcomes were corrected for the several potential confounders, such as the use of chemotherapy and endocrine treatment.

An overall conclusion of the research summarised in this thesis is that young women with early stage breast cancer can be treated safely with breast-conserving therapy with regard to local control and survival. In our cohort, no additional short-term treatment-related toxicities were reported in these young women treated with 3D-CRT. However, the very long-term toxicities should be monitored and evaluated as well, since these might be less favourable. Finally, although initially present, on the medium long-term, young women treated with radiotherapy for breast cancer were not at risk for decreased quality of life, based solely on age.

## Future perspectives

The recent decades, the treatment of breast cancer has become more and more complex, consisting of several treatment modalities based on an increasing number of individual risk factors. In general, prognosis of breast cancer has improved due to several factors. Next to diagnosis in earlier stage by enhanced cancer awareness and screening, prognosis has improved by optimisation of the individual treatments and the combination of this multimodality treatment [6]. Patients with higher risk of local recurrence or distant metastases, such as young age, negative receptor status and lymph node positivity, receive different combinations of systemic therapy and radiotherapy.

In breast radiotherapy, this stratification is used to select patients for specific hypofractionation schedules. The hypofractionation schedules used at our department have been adapted several times according to the most recent findings. In 2011, more extensive hypofractionation schedules were introduced, and a large proportion of the patients without extra risk factors for LRR started with these fractionation schedules. In the future, the standard follow-up programme (SFP) can be used to evaluate these new hypofractionated irradiation schedules in terms of outcome, toxicity and quality of life.

Stratification based on clinical risk factors is the first step towards truly individualized medicine based on molecular profiling. It will be increasingly difficult to design randomized controlled trials (RCTs) that can address the complexity of tumour and patients heterogeneity, resulting in numerous subgroups with few patients included. These small numbers may hamper interpretation of outcomes and RCTs, which are still considered the gold standard, may no longer be feasible. Therefore, large prospective observational cohorts, such as the SFP initiated at our department, will become increasingly important. These cohorts are preferably assessed multi-centre, with uniform covariates and definitions to build large databases for analysis.

At present, even in young women, prognosis after breast cancer diagnosis – especially among patients with early stage tumours – is generally favourable, with 5-year survival rates for stage I-II of more than 92% [39]. Young breast cancer survivors are longer at risk than older patients for developing treatment-related side effects. The toxicities reported in Chapter 5, in part transient (oedema) and in part persisting (fibrosis), are probably not the most relevant after radiotherapy for breast cancer. With improved survival, the late side effects with a long latency, such as cardiac complications and the development of secondary tumours, will become increasingly important. The follow-up of our study was too short to evaluate these harmful side effects. These long-term complications have to be monitored carefully and should be subjected to further study.

In this thesis, we reported on research concerning risk factors for developing treatment-related side effects. The models used in these studies were based on patient, tumour and basic treatment parameters only. However, the collected data, further completed with dose distribution data of organs at risk ((OAR) normal tissue) can be used to develop multivariable Normal Tissue Complication Probability (NTCP) models. This is the most direct in vivo method to investigate the relationship between dose distribution parameters and radiation-induced side effects, a dose-effect relationship. Currently, a study with the aim to develop an NTCP model for fibrosis of the breast after radiotherapy as part of BCT is ongoing at our department.

With these NTCP models, the risk given a certain dose to the organ of interest, of developing certain complications after radiotherapy can be assessed for individual patients. Recently, Darby *et al.* [40] reported on the risk of ischemic heart disease after radiotherapy for breast cancer. This study showed that with every Gray increase in mean heart dose, the risk of a major coronary event increased with 7.4%, added to the risk of pre-existing cardiac risk factors of a specific patient. This additional risk started within the first 5 years after radiotherapy and continued more than 30 years. In this thesis, we tried to establish the safety of breast-conserving therapy in young women. With the data generated at our department, the model by Darby *et al.* can be validated in our own cohort with a specific patient mix. Estimating long term cardiac risks is especially important in the group of young women treated with radiotherapy, since these risks should not counterbalance the benefits of adjuvant radiotherapy.

In the future, the NTCP models will probably become even more specific in estimating the individual risk for treatment-related side effects. In this very advanced modelling, a patients' biologic susceptibility can be integrated in the risk assessment. An example is the inclusion of single-nucleotide polymorphisms (SNPs) in the model [41]. By identifying SNPs associated with intrinsic radiosensitivity, resulting in treatment-related side effects, one could differentiate between patients suitable for radiotherapy. Patients eligible for BCT or for mastectomy could be identified, but also patients with a very low risk of local recurrence could be advised to be treated with breast-conserving surgery without radiotherapy.

Besides traditional whole breast radiotherapy combined with a boost dosage to the surgical bed, other radiotherapy strategies have been developed in the last decade as part of BCT. The aim of these strategies was to achieve the same local control, but with fewer side effects and decreased overall treatment time compared to whole breast irradiation. One example is partial breast irradiation, in which the target volume consists of the surgical bed with a certain margin. Radiation can be applied with external beam irradiation, intraoperative or a brachytherapy device can be used. With brachytherapy, accelerated partial breast irradiation (APBI) can be performed using a balloon catheter inserted after lumpectomy, such as the MammoSite [42]. In appropriate selected patients with low risk of local recurrence, such as small tumour, no or few positive lymph nodes, clinically unifocal disease and negative surgical margins, APBI is currently the subject of ongoing phase III trials. The latest data suggest promising 5-year outcomes, with a local control of 96.2% and 90.5% excellent to good cosmetic result [43]. Since young women are at higher risk for local recurrence, partial breast irradiation might not be the best strategy in young women.

Another potential strategy in BCT is radiotherapy with protons. Relative to photon therapy, irradiation with protons potentially results in a reduced dose to normal tissues and reduced treatment-related side effects, with the same tumour

control probability. These benefits are due to the superior beam properties of proton therapy. The greatest challenge will be the selection of patients for proton therapy, since its higher costs and limited availability will restrain the use of protons for breast cancer treatment. The goal is selecting the patients who are expected to benefit most from radiotherapy with protons in terms of reducing the risk of radiation-induced side effects. This can be achieved by using the model-based approach as described by Langendijk *et al.* [44].

In breast cancer, patients who potentially benefit from protons are those in whom the dose to the OAR with photons is too high, with unacceptable risks for toxicity. One group of patients potentially benefitting might be young women. Based on recently published abstracts [45-47], the indications for locoregional radiotherapy are expected to be extended by several more years. Considering that locoregional radiotherapy adds to the risk of long-term toxicity, proton therapy might be beneficial in these cases. Other cases might be patients who need bilateral radiotherapy or patients with a pectus excavatum, especially in young women. This will be investigated further.

In this thesis, we have shown that young women are not specifically at risk for reduced quality of life after breast cancer treatment. However, this statement is based on mean results in groups of patients and corrected for potential confounders. Since majority of young women are treated with chemotherapy and endocrine treatment, the impact of these factors on HRQoL need to be considered as well. The next step is the analysis of patient-specific risk profiles. One might be able to identify a specific subgroup of young breast cancer patients, who indeed are at risk for long term decreased quality of life. Subsequently, these women can be identified pre-treatment and possibly offered interventions to prevent issues causing decreased quality of life.

In conclusion, breast-conserving therapy with 3D-CRT-SIB is suitable for young women with early stage breast cancer, with excellent clinical outcomes, acceptable short-term toxicities and good quality of life.



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